(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 October 2005 (13.10.2005)

PCT

(10) International Publication Number
WO 2005/095622 A2

(51) International Patent Classification[7]: C12N 15/86

(21) International Application Number:
PCT/US2005/010441

(22) International Filing Date: 28 March 2005 (28.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/556,473 26 March 2004 (26.03.2004) US

(71) Applicant *(for all designated States except US)*: **VAN ANDEL RESEARCH INSTITUTE** [US/US]; 333 Bostwick Avenue, NE, Grand Rapids, MI 49503 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SHINOMIYA, Nariyoshi** [JP/JP]; National Defense Medical College, Department of Microbiology, 3-2 Namiki, Tokorozawa, Saitama, 359-8513 (JP). **VANDE WOUDE, George, F.** [US/US]; 9451 Bailey Drive NE, Ada, MI 49301 (US).

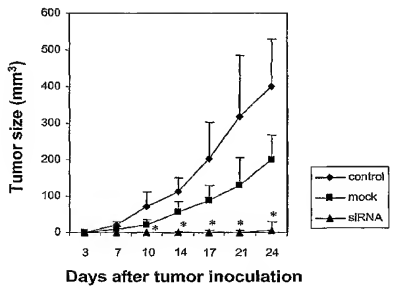
(74) Agent: **SHMUEL, Livnat**; McKenna Long & Aldridge LLP, 1900 K Street , N.W., Washington, DC 20006 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

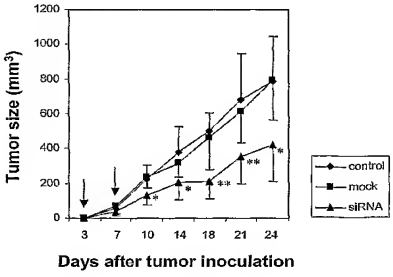
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: *c-met* siRNA ADENOVIRUS VECTORS INHIBIT CANCER CELL GROWTH, INVASION AND TUMORIGENICITY



A



B

(57) Abstract: Suppression of the Hepatocyte growth factor/scatter factor (HGF/SF)-Met signaling pathway by targeting the Met protein tyrosine kinase was tested as strategy for suppressing tumor growth. Using RNA interference (RNAi) technology and adenoviruses carrying siRNA (Ad Met siRNA) target sequences dramatically reduced Met expression in mouse, dog and human tumor cells. Met was suppressed using Ad Met siRNA in mouse mammary tumor (DA3) cells and Met-transformed (NIH3T3 (M114) cells as well as human prostate cancer, sarcoma, glioblastoma, gastric and ovarian cancer cells. Furthermore, the Ad Met siRNA infection reversed transformed cell morphology. Ad Met siRNA killed cancer cells by inducing apoptosis. RNAi targeting Met suppressed HGF/SF-mediated scattering as well as ligand-mediated invasion activity and growth of tumor cells. Met siRNA infection also abrogated downstream Met signaling to molecules such as Akt and p44/42 MAPK. Importantly, the Met siRNA triggered apoptosis was correlated to suppressed tumorigenicity in vivo. Intro-tumoral infection with c-met siRNA adenovirus vectors produced significant reduction in tumor growth. Thus Met RNAi is an effective weapon for targeting Met expression and for treating c-Met$^+$ cancers.

WO 2005/095622 A2

GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.